This Month in *The Journal*

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DASHing to Find IBD

Gusev et al., page 706

These days, people are in a big hurry to uncover rare variants that associate with common diseases. Testing for single rare variants in a population is complicated by the sheer number of people needed to provide power for such studies. Thus, many groups have moved to looking at multiple common markers that might collectively tag rare variants. These haplotypes are considered to have identity by descent (IBD). Current methods have largely focused on short haplotypes (20 SNPs or less) containing variants known to associate with the disease of interest. These methods rely on imputation to complete haplotypes, and this imputation in turn relies on the use of appropriate reference panels. For many studies, the HapMap populations can be (and often are) used. However, detecting low-frequency alleles in outlying populations not yet included in these reference panels has remained beyond the scope of powerful imputation and IBD studies. An alternative to imputation of short haplotypes is to focus on long genomic segments that are identical by state. Although this type of study works well, it cannot yet be used on a genome-wide scale. In this issue, Gusev and colleagues have devised an algorithm, DASH, to construct identical-by-descent genomic segments useful for genome-wide association studies (GWASs) without depending on a reference panel, making this method useful for both common and outlier populations. To demonstrate the power of DASH, the authors conduct a GWAS for rare variants associated with different traits in a Micronesian population isolate. Not only do they detect previously reported associations, but they also find and replicate additional risk alleles. Thus, DASH is quickly leading the field in the right direction.

Selecting to Avoid Malaria Infection

Ko et al., page 741

Genetic selection comes in different varieties. Although most alleles are thought to evolve via neutral selection, or the change that occurs in a gene pool as a result of random variation, other types of selection are at play throughout our genome. Depending on the advantage or disadvantage for survival, one can select for (positive selection) or against (negative selection) alleles. Likewise, intermediate and extreme traits can be selected for via stabilizing and disruptive selection, respectively. Balancing selection is yet another variety. With this type of selection, multiple alleles are maintained in the gene pool. Probably the best known example of balancing selection is the maintenance of alleles that cause sickle-cell disease (SCD), an autosomal-recessive genetic condition that remains prevalent in populations originating from regions where malaria is or was common. The same *HBB* alleles that cause SCD in a recessive state protect against malaria in a heterozygous state. However, hemoglobin is not the only factor determining the outcome of malaria infection, and *HBB* might not be the only gene that has undergone selection due to malaria. In this issue, Ko and colleagues study the genetic selection acting on *GYPA* and *GYPB*, encoding two glycohporin receptors involved in malaria infection. Their investigation confirms selection at *GYPA* and reveals a signature of adaptive selection for *GYPB* alleles. Identifying these sites of adaptive change is helpful in elucidating functional variants involved in malaria infection and sheds new light on the relationship between host and parasite.

Little Orphan Diseasome

Zhang et al., page 755

Orphan diseases, officially defined as those diseases that affect fewer than 6.5 per 10,000 individuals in the US, create a difficult problem for the scientific research and medical communities: On one hand, the diseases are so rare that spending a large amount of time and money studying them can be difficult to rationalize, but on the other hand, there are so many such diseases that they collectively affect a large number of people. One approach that might make tackling this problem easier is to establish connections between orphan diseases. If common elements are determined to be involved in a number of diseases, then it might be possible to manage that group of diseases in a singular fashion. In addition, finding correlations would improve understanding of the underlying biology of the systems involved. In this issue, Zhang and colleagues create a network of orphan diseases and the genes that are mutated in them by considering functional similarities, interaction information, and connections described in the literature. The authors are then able to conclude that the genes mutated in orphan diseases tend

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to serve as essential hubs in their network, and on the basis of the high connectivity between different orphan diseases and the genes mutated in them, the authors suggest that the shared pathways and mechanisms implied by this connectivity will serve as universal targets for treatment.

Uprooting the Y Chromosome

Cruiciani et al., page 814

The Y chromosome is a valuable resource for studies of human evolution and migration. Certain regions of Y chromosome sequence have a relatively low level of diversity, and analyzing the changes that are present can contribute to the understanding of the demographic history of populations. By comparing the variants found on different Y chromosomes, researchers can map out the Y chromosome lineage through time by building a phylogenetic tree. As sequencing technologies have improved, new branches have been added as the identification of additional variants has led to increased resolution between samples, but a close re-examination of the backbone and root of the Y chromosome phylogeny has been lacking. In this issue, Cruciani and colleagues perform a detailed analysis of samples representing these pieces. Their findings allow them to make important changes to the accepted structure of how groups of Y chromosomes relate to each other and also to significantly modify estimates of the timing and location of the origin of the Y chromosome lineages. These differences supported by the revised phylogenetic tree will contribute to the understanding of early modern human evolution.

Pulling Back the Cloud of Cataracts

Chen et al., page 827

Cataracts are disorders in which disruption of lens transparency renders the lens opaque and causes vision loss. Congenital cataracts (CC) are responsible for approximately one third of cases of blindness in infants worldwide. The disorder is very heterogeneous, and more than 40 loci have been identified for syndromic and nonsyndromic forms. Here, Chen and colleagues report their study of a large dataset of Pakistani families affected by autosomal-recessive CC to identify the mutated gene. After performing linkage analysis and screening candidate genes, Chen et al. found *FYCO1* mutations in 13 families. FYCO1 has been shown previously to associate with autophagosomes and has been predicted to be involved in the trafficking of these organelles within cells. Cellular localization work here supports that finding, and the authors hypothesize that it is the disruption of authophagy in these patients that leads to the accumulation of cellular products in the lens that disrupt lens transparency. If the dataset evaluated here is representative of Pakistanis with autosomal-recessive CC, mutations in *FYCO1* might be the cause of 10% of cases in that population.